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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

**Continuation Sheet**

**Item 5**

In light of applicants' amendments to the claims, the claim objection to the instant claims 1 and 5 is withdrawn.

In light of applicant's argument pointing to the support in the instant disclosure for the previously added new claim features (Reply, pp.13+), the following claim rejection is withdrawn:

Claims 1 and 17 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. (New Matter Rejection).

In light of applicant's argument pointing to the antecedent basis in the instant claims (Reply, p.15), the following claim rejection is withdrawn:

Claim 5 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention

**Item 11**

The following outstanding claim rejection is maintained for reasons of record:

Lerner and Brenner

Claims 1, 3-10 and 15-30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lerner et al (US 5,573,905; 11/12/1996), in view of Brenner (US 5,635,400; 6/3/1997; cited previously).

Applicant's traversal over the above claim rejection is considered, but is found not to be persuasive. Applicants argue the combination of the Lerner and Brenner references are through hindsight reasoning (Reply, p.16, last para).

In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

In this case, the motivation to combine the cited references are not gleaned from applicant's disclosure, but are from the art as well as from knowledge within the level of ordinary skill at the time the claimed invention was made.

In addition, applicants are also respectively directed to the recent Supreme Court decision, which forecloses the argument that a specific teaching, suggestion, or motivation is required to support a finding of obviousness. *KSR, 127 S.Ct. at 1741, 82 USPQ2d at 1396*.

Applicants also argue "the rejection fails to demonstrate why or how these fragmented aspects would have led one of ordinary skill to Applicant's claimed invention taken as a whole." (Reply, p.16, last para). Contrary to applicant's assertion, the previous Office action (mailed 2/7/08; pp.11+) have provided statements for reasons and motivations to combine the references' teachings.

Applicants also seem to argue that the combination of the cited references do not teach all elements. (Reply, pp.17+).

Applicants state "Lerner's 'sequential encoding' process begins with encodes nothing and cannot be used to pre-encode or direct the synthesis of a compound by any hybridization-based splitting strategy." (Reply, p.17, para 3).

First, the above cited statement is traversing the rejection by attacking the Lerner reference alone. As state in the previous office action as well as acknowledged by applicant's, the Brenner reference was cited to remedy the Lerner's lack of explicit teaching of "splitting" by hybridization to immobilized complementary oligonucleotides. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Second, applicant's statement of "Lerner's 'sequential encoding' process begins with encodes nothing and cannot be used to pre-encode or direct the synthesis of a compound" is not clear. Applicants have not provided supporting evidence to show that the process "begins with encodes nothing and cannot be used to pre-encode..." It is not clear how the method steps of the

Lerner reference in combination with Brenner are different from the steps of the instant claims. Applicants also seem to argue the only the completed synthesized oligonucleotides can "encode". The instant specification did not provide an explicit and specific definition for oligonucleotides that can "encode". As the term is broadly used, the partially synthesized oligonucleotides of the Lerner reference can "encode" for the attached amino acid residues (see Figure 2 of Lerner, for example). Applicants also acknowledged the fact that the oligonucleotides sequence of the Lerner reference code for the attached chemical unit (see Reply, p.17, para 2). Even if the initial synthesis (both oligonucleotide attachment and chemical unit attachment to the "linker") of the Lerner reference does read on a method using a single stranded nucleic acid tag, the subsequent steps of the Lerner reference reads on method steps of using "a single stranded DNA sequence" (see Lerner, Figure 2, after step 1).

Applicants also state "Brenner adds nothing to Lerner". (Reply, pp.17+). Applicants are respectfully directed to the previous office action for explanation of how the combination of the Brenner and the Lerner references render the instant claimed invention obvious.

Applicants again traversed over the Brenner reference by arguing the initial attaching step does not read on the method steps of the instant claims. (Reply, p.18). First, the Brenner reference was cited to supply the teaching of using solid support immobilized complementary oligonucleotides for the splitting (or sorting) steps, as discussed in the previous office action. In addition, the subsequent steps attaching chemical compounds (after the initial steps) would read on the instant method steps of using a single stranded nucleic acid.

Applicants also argue because the Brenner reference teaches "sorting" the oligonucleotides "after" synthesis, the Brenner reference does not teach "the use of immobilized

oligonucleotides to sort or split complementary oligonucleotides as an integral part of a method of making the compound library to begin with". (Reply, p.18, para 4). First, again, applicants have traversed the above rejection by attacking the Brenner reference alone. Applicants seem to argue because the Brenner reference doesn't teach all elements, the above said rejection should be withdrawn. However, the above rejection is over the combination of references.

Applicants have not provided any reason as to why it would not be obvious to use the immobilized oligonucleotides (or the method of using immobilized oligonucleotides) of the Brenner reference to sort complementary DNA that is used as the "nucleic acid tag" of the Lerner reference.

Applicants also argue the instant claimed methods require "pre-encoded nucleic acid tags" that "require absolutely no further nucleic acid sequences be added or removed..." (Reply, p.19, para 3). Contrary to applicant's assertion, the above cited feature is not recited in the instant claims. In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., pre-encoded nucleic acid tags" that "require absolutely no further nucleic acid sequences be added or removed...") are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

The instant claims recite the open-ended transition phrase "comprising", which term does not exclude other method steps. For example, the step of adding nucleic acid residues onto the "nucleic acid tags" is permissible in the instant claims.

Applicants also seems to argue with "mixing" (or pooling of the nucleic acid tags), the "purpose of Brenner's sequencing method" would be destroyed (Reply, p.20, para 3). However, the Brenner reference was not cited as the primary reference to be modified. Again, the Lerner reference was cited for teaching split and pool synthesis to form nucleic acid tagged molecules as discussed in the previous office action. The Lerner reference does not explicitly teach using immobilized oligonucleotides to sort (or split) the produced nucleic acid tagged molecules. The Brenner reference teaches using immobilized oligonucleotides for sorting (or splitting) nucleic acid molecules. The combination of the Lerner reference (teaching all other method steps) with Brenner reference (teaching the specific splitting step) would not render the intended purpose of the Lerner reference (e.g. split, sorting and pooling nucleic acids) unsatisfactory, and change the principle of operation of the Lerner reference. (See MPEP 2143.01.)

Applicants also assert "the Examiner mischaracterizes Lerner and Brenner and Applicant's claimed method in an in appropriate attempt to apply disjointed fragments of these references against various other specific steps of the subject claims". (Reply, pp.21+).

In general, applicants traversed the rejection by attacking each cited reference alone. Applicants traversed all the citations of the Lerner's reference by asserting Lerner does not teach "hybridization-based splitting". As discussed above and in the previous office action, the Brenner reference is supplied to remedy the non-explicit teaching of Lerner in term of using immobilized oligonucleotide for hybridization based splitting (or sorting) step.

The instant claim language is broad and encompassing various method steps and reagents. Applicants again argue for limitations such as "pre-coded" which are not recited in the instant claims. As discussed above and in the previous Office action, the broad claim language of

the instant claims encompasses the teachings of Lerner and Brenner references. Applicants have not provided any genuine distinction between the instant claimed method and the references' teachings.

Applicants state "Applicant disagrees with the Examiner's assertion that the nucleotide extension reaction and terminal nucleotides of Lerner somehow reads on the subject claims." (Reply, pp. 21-22, bridging). However, applicants made the above state without providing reasons to indicate why the nucleotide extension reaction of Lerner would not read on the "chemical reaction" of the instant claim. It is noted that applicants do not dispute the reason provided in the previous office action for the said teaching from Lerner.

Applicants further state "That Applicant's method employs nucleic acids that can be modified on the 5' or 3' ends with other nucleotides has no bearing on the claimed invention as a whole". (Reply, pp. 21-22, bridging). It is not clear what applicants are trying to convey by this statement. The instant claims (e.g. Claim 1) recites "said 5' terminus is covalently attached to a chemical reaction site", which site is subjected to a chemical reaction. The terms "chemical reaction" and "reagents" are not specifically defined in the instant specification, and thus, the instant claims broadly encompassing various chemical reactions using various reagents including nucleotide addition reactions using nucleotides.

Applicants also assert the term "variable hybridization sequences" is specifically defined in the instant specification. (Reply, p.23, para 2). Applicants provide "Figure 1, specification page 6, lines 29-32, and page 12, lines 30-32) for definition of "variable hybridization sequences". The cited Figure and recitations of the instant specification do not provide a limiting definition for the term "variable hybridization sequences" that would distinguish the said



sequences over the sequences of the prior art. For example, on page 12, the instant specification states "variable" refers "to the hybridization sequences which are different for each group of subsets of nucleic acid sequences". This said definition of "variable sequences" is broad and encompasses any nucleic acid sequence.

Applicants also argue the references' teachings do not read or render obvious of the "catenated nucleotide sequences" as recited in the instant claims 22 and 30. Applicants are respectfully directed to the previous rejection for detailed discussion on the reference's teachings. Applicants again traversed the rejection by arguing limitations (i.e. Reply, p.26, bottom of para 3) not recited in the instant claims.

/SUE LIU/

Examiner, Art Unit 1639

/Jon D. Epperson/  
Primary Examiner, AU 1639